REMARKS

I. Note to the Examiner

Applicants respectfully bring to the Examiner's attention pending U.S. application Ser. No. 09/447, 939, which is a bypass continuation, filed November 23, 1999, of International Application No. PCT/US99/11497. The instant application is a national stage application filed under 35 U.S.C. § 371 of International Application No. PCT/US99/11497.

II. Comments on Restriction Requirement

The Examiner maintained the restriction requirement and made it final (Office Action, pages 2-4). The Examiner alleged that the requirement to elect a single polypeptide and its encoding polynucleotide was proper because "[i]nstant case, claims multiple polynucleotide sequences and polypeptide sequences, which constitutes a recitation of an implied, mis-joined Markush group that contain multiple, independent and distinct inventions" and that "[t]he polypeptides and the polynucleotides claimed in the instant application, do not have a common property or activity because the relationship between a function and 'SOCS box' is not determined as yet" (Office Action, page 3.)

Applicants do not agree with the Examiner. However, in order to expedite prosecution, Claims 21, 22, 29, and 37 have been amended to remove SEQ ID NO:1-4 and SEQ ID NO:6-9 and Claims 25 and 31 have been amended to remove SEQ ID NO:10-13 and SEQ ID NO:15-18.

Claims 33-35 are "method of use" claims which depend from product Claim 31, and Claims 38-40 are "method of use" claims which ultimately depend from product Claim 21. Therefore, upon allowance of Claim 31, it is believed that Claims 33-35 should be rejoined and considered, and upon allowance of Claim 21, it is believed that Claims 38-40 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b).

III. Objection to Claims 21-29, 31-32, and 36-37

The Examiner objected to Claims 21-29, 31-32, and 36-37. In particular, the Examiner objected to Claims 21, 22, 25, 29, 29, 31, and 37 because they "recite non-elected sequences" and

to Claims 23-24, 26-28, 32, and 36 "in so far as they depend on claims 21 and 31." (Office Action, page 4.)

In order to expedite prosecution, Claims 21, 22, 29, and 37 have been amended to remove SEQ ID NO:1-4 and SEQ ID NO:6-9 and Claims 25 and 31 have been amended to remove SEQ ID NO:10-13 and SEQ ID NO:15-18. Therefore, Applicants respectfully request that the Examiner withdraw the objection to Claims 21-29, 31-32, and 36-37.

IV. Objections to the Specification

A. Prior Application Reference

The Examiner objected to the Specification with respect to a reference to the international application of which the instant application is the national stage. (Office Action, page 4.)

The Specification is amended to insert a reference to the prior international application.

B. Abstract

The Examiner objected to the Specification, stating that "[t]his application does not contain an abstract as required by 37 CFR 1.72(b). An abstract on a separate sheet is required." (Office Action, page 5.)

Applicants submit that the application as filed contains a proper abstract. The abstract is found on the front page of the pamphlet published by WIPO for International Application No. PCT/US99/11497, filed May 25, 1999 and published in English as WO 99/61614 on December 2, 1999.

The MPEP under § 608.01(b), Abstract of the Disclosure, states that:

> The abstract must commence on a separate sheet, preferably following the claims, under the heading "Abstract of the Disclosure." Form paragraph 6.16.01 (below) may be used if the abstract does not commence on a separate sheet. **Note that the abstract for a national stage application filed under 35 U.S.C. 371 may be found on the front page of the Patent Cooperation Treaty publication (i.e., pamphlet). See MPEP § 1893.03(e).** (emphasis added.)

The MPEP under § 1893.03(e), Papers Received from the International Bureau and Placed in a U.S. National Stage Application File, states that:

> The national stage application includes papers forwarded by the International Bureau and papers from applicant. Some of the papers from the

International Bureau are identified in this section with a brief note as to their importance to the national stage application. The examiner should review each such paper and the important aspect indicated.

THE PAMPHLET

The Pamphlet includes

(A) a cover page with the applicant/inventor data, the application data (serial number, filing date, etc.)
and the Abstract (and, if appropriate, a figure of drawing),

(B) the description, claims and drawing parts of the international application, and

(C) the search report (Form PCT/ISA/210).

The cover page is important as a source of the correct application data, most importantly the filing date and priority date accorded to the international application. If the pamphlet is published in English, applicant need not submit a copy of the international application to the Patent and Trademark Office. **The Office will use the description, claims, abstract and drawings as published in the pamphlet for the U.S. national stage examination under 35 U.S.C. 371.** The description, claims and drawing parts of the international application reflect the application subject matter on the international filing date and are important for comparison with any amendments to check for new matter. The search report reflects the International Searching Authority's opinion regarding the prior art.

>When the international application is published as the pamphlet, the abstract is reproduced on the cover page of the publication, even though it appears on a separate sheet of the international application in accordance with PCT Rule 11.4(a). Thus the requirement of 37 CFR 1.52(b) that the abstract "commence on a separate sheet" does not apply to the copy of the application (pamphlet) communicated to the designated Offices by the International Bureau under PCT Article 20. Accordingly, it is improper for the examiner of the U.S. national stage application to require the applicant to provide an abstract commencing on a separate sheet if the abstract does not appear on a separate sheet in the pamphlet.** Unless the abstract is properly amended under the U.S. rules during national stage processing, the abstract that appears on the cover page of the pamphlet will be the abstract published by the USPTO under 35 U.S.C. 122(b) and in any U.S. patent issuing from the application.< (emphasis added.)

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objections to the Specification.

V. Rejection of Claims 21-29, 31-32, and 36-37 Under 35 U.S.C. § 101

SUMMARY OF THE INVENTION

Applicants' invention is directed, *inter alia*, to a polynucleotide encoding a polypeptide ("HSCOP-5") having homology to a SOCS protein, both the polynucleotide and the polypeptide having a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of HSCOP-5, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 39, line 29 through page 44, line 22 and page 45, line 22 through page 46, line 8).

As described in Table 2 and in the Specification at page 5, lines 29-30 and page 16, lines 3-8, HSCOP-5 contains regions with homology to WD-40 repeats at L166-D199, L210-N242, L252-D284, contains a region with homology to a SOCS box at V384-I421, and is homologous to WSB-1. As described in Table 3 and in the Specification at page 5, line 31 through page 6, line 2 and page 16, lines 9-14, SEQ ID NO:14 is expressed in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues.[1]

Claims 21-29, 31-32, and 36-37 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Office Action, page 5.) In particular the Examiner alleges that "[t]he claimed invention . . . is directed to a polypeptide with no known activity" and that "[a]lthough instant specification asserts that claimed polypeptide can be used for diagnosis, treatment, or prevention of cancer, immune and neurological disorders and infectious diseases, (page 15, lines 20-24), it does not disclose how is the claimed polypeptide and polynucleotide can be used in these disparate diseases." (Office Action, pages 5-7.)

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[1]The Examiner states that "table 3 discloses that the polynucleotide of SEQ ID NO:14 is expressed in reproductive, cardiovascular and hematopoietic/immune system and that it is associated with cancer, inflammation, and neurological disorders." (Office Action, page 5.) Applicants note that Table 3 does not recite expression of SEQ ID NO:14 in tissues associated with neurological disorders.

The rejection of Claims 21-29, 31-32, and 36-37 is improper, as the invention of those claims has a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a gene that is expressed in human uterine endometrium tissue, as well as the polypeptide encoded by the polynucleotide. The polypeptide is identified in the patent application as a human SOCS protein, abbreviated as HSCOP-5. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of SOCS proteins, which function in cell signaling (Specification, pages 1-3.) The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the claimed polypeptide is a member of the SOCS protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide, as well as the polynucleotide encoding the polypeptide, also have patentable utility, regardless of the actual function of the claimed polypeptide. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this Response the Declaration of Dr. Tod Bedilion (hereinafter "the Bedilion Declaration") and the Declaration of Mr. Lars Michael Furness (hereinafter "the Furness Declaration") describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications.[2] The Bedilion Declaration and the Furness Declaration demonstrate that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide and polypeptide are without merit.

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[2]The Bedilion Declaration and Furness Declaration are filed herewith in unexecuted form. The executed Bedilion Declaration and Furness Declaration will be filed as soon as they are available.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on May 28, 1998] that cDNA microarrays that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

The Patent Examiner contends that the claimed polynucleotide and claimed polypeptide cannot be useful without precise knowledge of their biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion and Furness Declarations, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide and the claimed polypeptide encoded by the claimed polynucleotide n the absence of any knowledge as to the precise function of the claimed polypeptide. The uses of the claimed polynucleotide and claimed polypeptide in gene expression monitoring applications including toxicology testing are in fact independent of the precise function of the claimed polynucleotide and polypeptide.

A. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the

public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

B. Uses of the claimed polynucleotide and claimed polypeptide for diagnosis of conditions and disorders characterized by expression of HSCOP-5, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion and Furness Declarations accompanying this Response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The claimed polypeptide's membership in the SOCS protein family demonstrates utility

Because there is a substantial likelihood that the claimed HSCOP-5 is a member of the family of polypeptides known as SOCS proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:5 in the patent application and referred to as HSCOP-5 in that application. Applicants have demonstrated by more than reasonable probability that HSCOP-5 is a member of

the SOCS protein family, and that the SOCS protein family includes polypeptides which function in cell signaling. HSCOP-5 contains a region with homology to a SOCS box from residue V384 through I421 and contains regions with homology to WD-40 repeats at L166-D199, L210-N242, and L252-D284, and has homology to WSB-1 (Table 2 and Specification, pages 1-3).

The Examiner must accept the Applicants' demonstration that the claimed polypeptide is a member of the SOCS protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary. Nor has the Examiner provided any evidence that any member of the SOCS protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the SOCS protein family, useful.

Though not necessary to demonstrate the utility of the claimed SEQ ID NO:5 polypeptide, Applicants respectfully direct the Examiner's attention to the enclosed paper by D. Vasiliauskas et al., "SWiP-1: novel SOCS box containing WD-protein regulated by signalling centres and by Shh during development", Mech. Dec. (1999) 82:79-84 (Reference No. 1). This post-filing reference describes the characterization of a chick protein, termed cSWiP-1, which integrates two signals originating from structures adjacent to the segmental mesoderm: a positive signal from the notochord and a negative signal from intermediate and/or lateral mesoderm. The human homolog of cSWiP-1 is also described, which has 100% amino acid sequence identity to SEQ ID NO:5. (Alignment, Reference No. 2.) This post-filing reference confirms Applicants' prior identification of HSCOP-5 as a member of the SOCS protein family involved in cell signaling.

2. The uses of HSCOP-5 and the polynucleotide encoding HSCOP-5 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion and Furness Declarations. The claimed polynucleotide is a useful tool in cDNA microarrays used to perform gene expression

analysis. The claimed polypeptide is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. That is sufficient to establish utility for the claimed polynucleotide and the claimed polypeptide encoded by the claimed polynucleotide.

The instant application (the Lal '232 application) is the National Stage of International Application No. PCT/US99/11497, filed May 25, 1999 in the name of Preeti Lal et al., and published in English as WO 99/61614 on December 2, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional applications U.S. Ser . No. 60/087,104, filed May 28, 1998 in the name of Preeti Lal et al. (hereinafter the Lal '104 application) and U.S. Ser. No. 60/150,701, filed December 17, 1998 in the name of Preeti Lal et al. The provisional applications provide support for what is disclosed in the instant Lal '232 application. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. The SEQ ID NO:5 polypeptide is referred to as HSCOP-5 in the instant Lal '232 application and as SOCP-5 in the priority Lal '104 application.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Lal '104 application on May 28, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[3]

In connection with his explanations, Dr. Bedilion states that the " Lal '104 application would have led a person skilled in the art on May 28, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer,

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[3]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '104 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

immune disorders, and infectious diseases to conclude that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the Lal '232 application SEQ ID NO:14 polynucleotide." (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on May 28, 1998] that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool than a cDNA microarray that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-May 28, 1998 publications showing the state of the art on May 28, 1998 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include more than three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on May 28, 1998 (and for several years prior to May 28, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Lal '104 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '104 application at the time it was filed "would have wanted their cDNA microarray to have a [Lal '232 application SEQ ID NO:14 polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to May 28, 1998." (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '104 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on page 44, lines 10-22 and page 53, lines 1-21 of the instant application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed polynucleotide is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-May 28, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '104 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays

> disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the Lal '104 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
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> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original.)

John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, (July 1999) Xenobiotica 29:655-691 (Reference No. 3).

In a pre-May 28, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed polynucleotide and polypeptide are in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be

> used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 4).

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Lal '104 application. . . , the Wilkins article, and other related pre-May 28, 1998 publications, persons skilled in the art on May 28, 1998 clearly would have understood the Lal '104 application to disclose the SEQ ID NO:5 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶ 10)
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> * * *
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> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:5 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with

> conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, page 26).

3. The uses of nucleic acids coding for proteins expressed by humans and of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease are now "well-established"

The technologies made possible by expression profiling using polynucleotides and polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion and Furness in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 3):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 3), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 5); Sandra Steiner and N. Leigh Anderson, Expression profiling in

toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 6).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology , Environ. Health Perspec. 107:681-685 (1999) (Reference No. 7, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 8) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an

award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

4. The Uncontested Fact That the Claimed Polynucleotide Encodes a Protein in the SOCS Protein Family Also Demonstrates Utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotide encodes for a protein having the sequence shown as SEQ ID NO:5 in the patent application and referred to as HSCOP-5 in that application. Applicants have demonstrated that HSCOP-5 is a member of the SOCS protein family, and that the SOCS protein family members function in cell signaling.

The Patent Examiner does not dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept Applicants' demonstration that the polypeptide encoded by the claimed invention is a member of the SOCS protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503

F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the SOCS protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the claimed polypeptide encoded by the claimed polynucleotide must be, like the other members of the SOCS protein family, useful.

5. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotide and claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

C. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific" or "substantial" utilities. (Office Action, page 5.) The Examiner is incorrect both as a matter of law and as a matter of fact.

1. The Precise Biological Role, Function, Or Activity Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological activity" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polynucleotide either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polypeptide either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity.

It may be that detailed information on biological function is necessary to satisfy the requirements for publication in some technical journals, but it are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion and Furness Declarations (at, *e.g.*, ¶¶ 10 and 15, Bedilion; ¶¶ 10-12, Furness), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person

of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function, role, or activity of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function, role, or activity for any claimed polynucleotide or polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological function, role, or activity of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the SOCS protein family, as well as the family of expressed polypeptides, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the SOCS protein family and the family of expressed polypeptides to HSCOP-5. In the Office Action, the Patent Examiner takes the position that, unless Applicants can identify which particular biological function within the class of SOCS proteins is possessed by HSCOP-5, utility cannot be imputed. To demonstrate utility by membership in the class of SOCS proteins, the Examiner would require that all SOCS proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[4]

The Examiner addresses HSCOP-5 as if the general class in which it is included is not the SOCS protein family and the family of expressed polypeptides, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the SOCS protein family and the family of expressed polypeptides do not. The SOCS protein family and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that HSCOP-5 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the SOCS protein family and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed HSCOP-5 polypeptide is useful. It follows that the claimed polynucleotide also is useful.

3. Because the uses of HSCOP-5 and a polynucleotide encoding HSCOP-5 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed polynucleotide or claimed polypeptide. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed polynucleotide or claimed polypeptide invention as a

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[4]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

tool are **not** used merely to study the claimed polynucleotide and claimed polypeptide themselves, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15, Furness Declaration at ¶ 12.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses in chromosome mapping and drug screening (Specification, page 44, line 23 through page 46, line 8).

D. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the

question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § V.C.2. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category

of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § V.C.2. Thus the Training Materials cannot be applied consistently with the law.

VI. Rejection of Claims 21-29, 31-32, and 36-37 Under 35 U.S.C. §112, first paragraph

A. To the Extent the Rejection of the Claimed Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Office Action, page 7). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

B. The Claimed Variants are Adequately Enabled

The Examiner further contended that "[s]hould Applicants establish an activity for the polypeptide of SEQ ID NO:5, instant specification would still fail to adequately describe and enable an isolated polypeptide comprising an amino acid that has at least 90% to the polypeptide of SEQ ID NO:5, or a biologically active fragment as recited in claim 21, or an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14." (Office Action, page 7.) In particular the Examiner alleges that

> Applicants do not teach which regions of said polypeptide are critical for the functional integrity of the polypeptide, neither do they teach an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14 that encodes the desired polypeptide. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a polypeptide having at least 90% sequence identity to SEQ ID NO:5, nor does the disclosure provide criteria that explicitly enable such critical features. With respect to "a biologically active fragment", limitation recited in claim 21, instant specification does not describe what biological activity is claimed, nor does it describe a fragment with any activity. The specification does not describe the structure of a fragment of the polypeptide of SEQ ID NO:5 that is active. There is no guidance in the specification as to how one of ordinary skill in the art would generate a polypeptide, other than that exemplified. (Office Action, pages 7-8.)

The claimed polynucleotides and polypeptides are enabled, i.e., they are supported by the Specification and what is well known in the art. In order to expedite prosecution, Claim 21 has been amended to remove the recitation of biologically active fragments of SEQ ID NO:5, and therefore the Examiner's rejection on the basis of biologically active fragments is moot.

1. How to make

SEQ ID NO:5 and SEQ ID NO:14 are specifically disclosed in the application (see, for example, pages 5-6 and page 15 of the Sequence Listing). Variants of SEQ ID NO:5 and SEQ ID NO:14 are disclosed, for example, on page 14, line 27 through page 15, line 18, and on page 17, lines 3-21. Incyte clones in which the nucleic acids encoding the human HSCOP-5 were first identified and libraries from which those clones were isolated are disclosed, for example, in Tables 1 and 4. Chemical and structural features of HSCOP-5 are disclosed, for example, in Table 2.

The Examiner alleged that "[t]o practice the instant invention . . . [would require] a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues of the disclosed polypeptide, which are required for functional and structural integrity of the claimed polypeptide or to determine all the possible polynucleotides comprising at least 90% identical to the polynucleotide of SEQ ID NO:14, which are encompassed by the claims." (Office Action, page 8.) However, Applicants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:5 and SEQ ID NO:14 and not by biological activity or "functional integrity." The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring" polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 40, line 24 through page 41, line 5) which can then be expressed to make polypeptide variants and how to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to the polynucleotide sequence of SEQ ID NO:14" scope and whether a given naturally occurring amino acid sequence falls within the "at least 90% identical to the amino acid sequence of SEQ ID NO:5" scope (e.g., page 11, lines 8-24, Example III at pages 48-49, and Table 5). In addition, determination of percent identity is well known in the art.

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 18, line 17 through page 19, line 22; page 20, line 8 through page 21, line 4; page 40, line 17 through page 41, line 13; and Example VI at page 52, lines 13-31. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:5, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:14. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO: 14 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:5 recited by the present claims using conventional techniques of recombinant protein production.

The making of the claimed polynucleotide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 18, lines 11-16, page 21, lines 15-20, and page 21, line 29 through page 22, line 1. The making of the claimed polypeptide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g, page 21, lines 15-20, page 22, lines 1-7, and page 22, line 13 through page 26, line 1.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

2. How to Use

The claimed polypeptide variants and polynucleotide variants are products of expressed genes. Therefore, these polynucleotide variants are useful for the same purposes as the polynucleotide comprising the polynucleotide sequence of SEQ ID NO:14 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 5. These polypeptide variants are useful for the same purposes as the polypeptide comprising the polypeptide sequence of SEQ ID NO:5. These utilities are described fully under the rejection under §101 (*supra*) of this

Response and in the Bedilion and Furness Declarations. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner argues that "Applicants do not teach which regions of said polypeptide are critical for functional integrity of the polypeptide." (Office Action, page 7.)

However, the Specification, along with what is well known to one of skill in the art, enable the use of the claimed polynucleotides and polypeptides in toxicology testing by virtue of their being expressed polynucleotides and polypeptides, regardless of their biological function, "functional integrity" or "activity." The Examiner has confused use with biological function.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides and polypeptides. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides and polypeptides.

C. The Claimed Variants are Adequately Described

The Examiner does not appear make a formal rejection of Claims 21-29, 31-32, and 36-37 under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. However, the Examiner, under the enablement rejection, states that "[s]hould Applicants establish an activity for the polypeptide of SEQ ID NO:5, instant specification **would still fail to adequately describe** and enable an isolated polypeptide comprising an amino acid that has at least 90% to the polypeptide of SEQ ID NO:5, or a biologically active fragment as recited in

claim 21, or an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14." (Office Action, page 7, emphasis added.) In particular the Examiner alleges that

> Applicants do not teach which regions of said polypeptide are critical for the functional integrity of the polypeptide, neither do they teach an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14 that encodes the desired polypeptide. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a polypeptide having at least 90% sequence identity to SEQ ID NO:5, nor does the disclosure provide criteria that explicitly enable such critical features. With respect to "a biologically active fragment", limitation recited in claim 21, instant specification does not describe what biological activity is claimed, nor does it **describe** a fragment with any activity. The specification does not **describe** the structure of a fragment of the polypeptide of SEQ ID NO:5 that is active. There is no guidance in the specification as to how one of ordinary skill in the art would generate a polypeptide, other than that exemplified. (Office Action, page 7-8, emphasis added.)

Given these statements by the Examiner, Applicants are unsure whether the Examiner intended to reject Claims 21-29, 31-32, and 36-37 under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. Applicants respectfully request clarification of whether Claims 21-29, 31-32, and 36-37 are rejected on the basis of written description. In any case, the claimed subject matter is adequately described. Furthermore, in order to expedite prosecution, Claim 21 has been amended to remove the recitation of biologically active fragments of SEQ ID NO:5, and therefore the Examiner's rejection on the basis of biologically active fragments is moot.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:5 and SEQ ID NO:14 are specifically disclosed in the application (see, for example, pages 5-6 and page 15 of the Sequence Listing). Variants of SEQ ID NO:5 and SEQ ID NO:14 are described, for example, at page 14, line 27 through page 15, line 18. In particular, the preferred SEQ ID NO:5 variants (at least about 80%, more preferably at least about 90%, and most preferable at least about 95% amino acid sequence identity to SEQ ID NO:5) are described, for example, at page 17, lines 3-6. In particular, SEQ ID NO:14 variants (at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to SEQ ID NO:14) are described, for example, at page 17, lines 14-19. Incyte clones in which the nucleic acids encoding the human HSCOP-5 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1 and 4. Chemical and structural features of HSCOP-5 are described, for example, in Table 2. Given SEQ ID NO:5, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:5 at least 90% identical to the amino acid sequence of SEQ ID NO:5. Given SEQ ID NO:14, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:14 at least 90% identical to the polynucleotide sequence of SEQ ID NO:14. The Specification describes (e.g., page 11, lines 8-24 and page 48, line 5 through page 49, line 20, and Table 5) how to use BLAST and other methods to determine whether a given sequence falls within the "at least 90% identical" scope.

There simply is no requirement that the claims recite particular variant polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants are defined in terms of SEQ ID NO:5 ("An isolated polypeptide selected from the group consisting of. . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5." The polynucleotide variants are defined in terms of SEQ ID NO:14 ("An isolated polynucleotide selected from the group consisting of . . . b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:14.")

Because the recited polypeptide variants are defined in terms of SEQ ID NO:5, and the recited polynucleotide variants are defined in terms of SEQ ID NO:5 and SEQ ID NO:14, the precise chemical structure of every polypeptide variant and every polynucleotide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 21 and 31 recites chemical structure to define the claimed genus:

> 21. An isolated polypeptide selected from the group consisting of. . .
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5. . .

31. An isolated polynucleotide selected from the group consisting of. . . :

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:14. . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5 and SEQ ID NO:14. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides recited by the claims. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078); Reference No. 9). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to SOCS proteins related to the amino acid sequence of SEQ ID NO:5. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as SOCS proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:5. The "variant language" of the present claims recites, for example, an isolated polypeptide "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5. . . " (note that SEQ ID NO:5 has 421 amino acid residues). This variation is far less than that of all potential SOCS proteins related to SEQ ID NO:5, i.e., those SOCS proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:5.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 28, 1998. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:5 and SEQ ID NO:14, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5 and SEQ ID NO:14. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides and polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. Rejection of Claims 21-29 Under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 21-29 under 35 U.S.C. §112, second paragraph, alleging that Claim 21 and Claims 22-29 which depend from Claim 21, were indefinite for reciting "biologically active fragment" as "it is unclear which biological activity is being referred to." (Office Action, page 9.)

In order to expedite prosecution, Claim 21 as amended does not recite "biologically active fragment." For at least the above reasons, Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-4646.

Please charge Deposit Account No. **09-0108** in the amount of **$ 110.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: June 23, 2003

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Enclosures:

1. Daniel Vasiliauskas et al., SWiP-1: novel SOCS box containing WD-protein regulated by signalling centres and by Shh during development, Mech. Dev. 82:79-84 (1999)
2. Alignment of SEQ ID NO:5 with g4754060
3. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999)
4. Deval A. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (August 1997)
5. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999)
6. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000)

7. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999)
8. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding
9. Steven E. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-6078 (1998)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The following paragraph has been added immediately after the title on page 1.

This application is a national stage application filed under 35 U.S.C. § 371 of International Application No. PCT/US99/11497, filed May 25, 1999 and published in English as WO 99/61614 on December 2, 1999, which claims the benefit of U.S. Provisional Application No. 60/087,104, filed May 28, 1998, and U. S. Provisional Application No. 60/150,701, filed December 17, 1998.

Paragraph beginning at page 3, line 21 has been amended as follows:

The invention features substantially purified polypeptides, human SOCS proteins, referred to collectively as "HSCOP" and individually as "HSCOP-1", "HSCOP-2", "HSCOP-3", "HSCOP-4", "HSCOP-5", "HSCOP-6", "HSCOP-7", "HSCOP-8", and "HSCOP-9" ["HSOCP-1", "HSOCP-2", and "HSOCP-3", HSOCP-4", HSOCP-5", HSOCP-6", HSOCP-7", HSOCP-8", and HSOCP-9"]. In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-9, and fragments thereof.

Paragraph beginning at page 21, line 21 has been amended as follows:

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HSCOP-encoding [HSOCH-encoding] sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

Paragraph beginning at page 32, line 2 has been amended as follows:

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HSCOP-specific [HSOCH-specific] single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Paragraph beginning at page 32, line 31 and ending on page 33, line 16 has been amended as follows:

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HSCOP. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of HSCOP-antibody [HSOCH-antibody] complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HSCOP epitopes, represents the average affinity, or avidity, of the antibodies for HSCOP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HSCOP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HSCOP-antibody [HSOCH-antibody] complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HSCOP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

Paragraph beginning at page 33, line 17 has been amended as follows:

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of HSCOP-antibody [HSOCH-antibody] complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

Paragraph beginning at page 46, line 14 has been amended as follows:

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way [was] whatsoever.

Paragraph beginning at page 46, line 18, has been amended as follows:

The entire disclosure of all applications, patents, and publications, cited above and below, and of US provisional applications 60/087,104 (filed May 28, 1998), and 60/150,701 [09/216,006] (filed December 17, 1998) are hereby incorporated by reference.

Paragraph beginning at page 53, line 23 and ending on page 54, line 1 has been amended as follows:

Sequences complementary to the HSCOP-encoding [HSOCH-encoding] sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HSCOP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HSCOP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HSCOP-encoding [HSOCH-encoding] transcript.

Paragraph beginning at page 57, line 4 has been amended as follows:

Naturally occurring or recombinant HSCOP is substantially purified by immunoaffinity chromatography using antibodies specific for HSCOP. An immunoaffinity column is constructed by covalently coupling anti-HSCOP [anti-HSOCH] antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Paragraph beginning at page 57, line 10 has been amended as follows:

Media containing HSCOP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HSCOP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/HSCOP [antibody/HSOCH] binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HSCOP is collected.

IN THE CLAIMS:

Claims 21, 22, 25, 29, 31, and 37 have been amended as follows:

21. (Once Amended) An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9],

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9], and

c) [a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-9, and

d)] an immunogenic fragment of the [a] polypeptide having the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9].

22. (Once Amended) An isolated polypeptide of claim 21 comprising the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9].

25. (Once Amended) An isolated polynucleotide of claim 24 comprising the [a] polynucleotide sequence [selected from the group consisting] of SEQ ID NO:14 [SEQ ID NO:10-18].

29. (Once Amended) A method of claim 28, wherein the polypeptide comprises the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9].

31. (Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the [a] polynucleotide sequence [selected from the group consisting] of SEQ ID NO:14 [SEQ ID NO:10-18],

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the [a] polynucleotide sequence [selected from the group consisting] of SEQ ID NO:14 [SEQ ID NO:10-18],

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

37. (Once Amended) A composition of claim 36, wherein the polypeptide comprises the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:5 [SEQ ID NO:1-9].